While on this subject of zoster and internal diseases I will take the opportunity to state that I had a case, in 1874, of œsophageal cancer that had, late in the disease and over its seat, a complicating zoster eruption encircling the left side of the chest at the margin of the ribs. The eruption, it seemed to me, might be caused by the cancer, as the œsophagus is located to the left of the border of the vertebræ, near the roots of the nerves.

In 1890 to 1893 I had quite a number of cases of influenza and catarrhal fever complicated with zoster, generally coming on with the less acute influenzal attacks. A number of my friends reported to me one or more attacks of the same kind in their cases of acute and subacute influenza.

The subject being, I believe, a new one, I shall feel repaid if the attention of future observers is called to this interesting condition.

THE CHANGES OCCURRING IN STRIPED MUSCLE IN THE NEIGHBORHOOD OF MALIGNANT TUMORS.[1]

BY FRANK P. ANZINGER, A.M., M.D.,
OF ANN ARBOR, MICH.

BY far the greater part of the investigations made during the last decade into the nature of malignant tumors have been along the lines of their supposed parasitic origin. Yet, with all of the immense effort and labor extended in this direction, we are to-day not one step nearer the solution of the problem of the etiology of these growths. There is no sufficient evidence to prove that the peculiar bodies found in carcinoma cells are parasites, either bacterial, protozoic or blastomycetic, each of which they have from time to time been confidently proclaimed to be. It must be acknowledged that we are no nearer the demonstration of this problem than we were ten years ago, and the oft-repeated failures should convince us that if malignant neoplasms are parasitic in origin we must arrive at the discovery of the parasite by following lines different from those hitherto pursued. In the meantime, while this field of research is being so largely worked, other aspects of the tumor problem are being more or less neglected, particularly those along chemical lines.

Very little work has been done with the comparative chemistry of tumor cells and cells of normal tissues, or with the chemistry of the products of tumor-cells. The changes occurring in the cells in the neighborhood of malignant tumors have also received but scanty attention.

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[1] From the Pathological Laboratory of the University of Michigan, Ann Arbor, Mich.

In 1867, Otto Weber made observations on cancer in the pectoral and sternomastoid muscles. He described the manner of growth of carcinoma into the muscle, the presence of cancer-cells in the muscle-fibres, and the destruction of the muscle as the result of suppuration, but the finer structural changes were not observed. As a result of his study he concluded that cancer-cells were derived from muscle-elements. In 1870, Volkmann described the appearances of cancer in the pectoral muscle, the manner of invasion of the muscle by cancer-cells, the formation of cancer nodules, and a peculiar change in the muscle protoplasm, to which he applied the term *lacunar erosion.* He pointed out the fact that this change was due to the pressure of cancer-cells, and concluded that carcinoma cells invade muscle, but do not originate from muscle-elements.

The first careful study of the minute changes occurring in striped muscle in the neighborhood of malignant growths was made by Schaeffer in 1886. The material examined by him consisted of 3 cases of epithelioma of the lip, 2 cases of carcinoma of the pectoral muscle, 3 cases of carcinoma of the tongue, and 4 cases of sarcoma. The manner of invasion of the muscle and the gross appearances of muscle changes are first described by him, then the finer changes as produced both by sarcoma and carcinoma. The special changes observed were: Distortion of the fibres, atrophy, cloudy swelling, fatty degeneration, waxy change, fissuring, changes in staining, nuclear proliferation, hypertrophy, small-celled infiltration, and increase of the perimysium. He compared these changes with those found in other conditions, and concluded that the changes produced by tumors were not characteristic, but could be produced by other pathological agencies.

Since the work carried out by these three observers represented the sum total that had been done in this direction, it seemed worth while to extend this research with a view to settling several questions left untouched by them, particularly with reference to a comparison of the changes produced by sarcoma and carcinoma. While this work was in progress there appeared in April, 1900, an article upon the same subject by Fujinami. As this is the last and most important contribution in this line, I give his conclusions somewhat at length. These are based upon the study of 20 cases of sarcoma and 17 of carcinoma infiltrating muscle. The manner of invasion and the changes occurring in the contractile substance and muscle nuclei, and the fate of the primitive muscle bundle, are considered in detail. The results of this study are as follows:

1. The invasion of the muscle takes place in different ways, both through the lymph-spaces, lymph- and bloodvessels, and the sarcolemma.

The invasion of the sarcolemma by tumor-cells occurs most frequently in the case of carcinoma, and is especially pronounced when the direction of extension of the tumor is parallel with the axis of the muscle-bundle. It is seldom seen in sarcoma, occurring only in the case of the small round-cell variety. The penetration of the sarcolemma is dependent upon the biological relations of the tumor-cells, their direction of growth, and the variety of change in the muscle-substance.

2. The changes in the primitive muscle-bundle are of manifold variety, all possible changes occurring. Simple atrophy is the most frequent; and the most interesting are the nuclear proliferation, "ampullar atrophy" and formation of giant-cells. Those changes formerly regarded as regenerative in nature are to be regarded as being essentially degenerative, the primitive muscle-bundle in a certain stage of retrogression assuming relations similar to those at the beginning of its development.

3. The muscle-fibres show varied and irregular changes in thickness and length.

4. The changes produced in the primitive muscle-bundle by tumor-cells cannot be referred alone to mechanical pressure, but the changed biological relations of these cells must also produce chemical effects.

5. In the interstitial connective tissue there is often a reaction, as shown by leucocyte infiltration, fibroblastic proliferation, and proliferation of the intima of the vessels. These changes may also secondarily affect the primitive muscle-bundles. The infiltration of the perimysium is usually much more marked in the periphery of carcinoma than of sarcoma.

6. Cell-forms (sarcolytes, sarcoplasts) arise from the changed muscle-bundles, and under certain conditions it is probable that these take part in the formation of tumor-cells.

7. A connective-tissue-like change of the muscle-fibres is assumed.

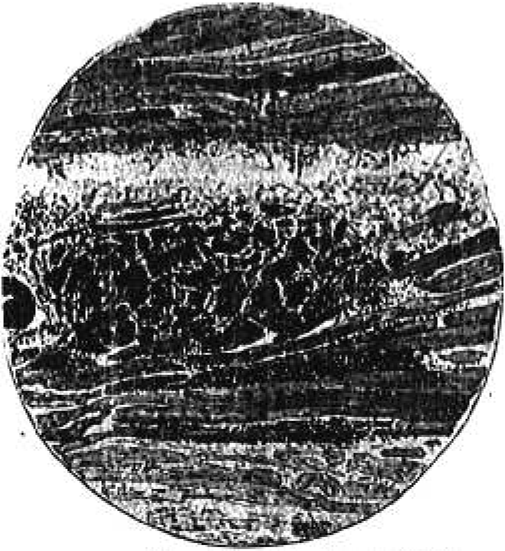
8. The reaction of muscle to the invasion of a malignant tumor may be very varied according to the local conditions. The muscle does not play a passive rôle simply.

9. The fact that the muscle-fibres possess a characteristic appearance and show various changes is of practical value in the diagnosis of tumors, in so far as it aids in establishing the biological properties of the tumor-cells and their direction of growth.

10. There is no absolute difference between the muscle changes produced by sarcoma and carcinoma.

As the work begun by me before the appearance of Fujinami's paper had led me to conclusions differing from some of those of his, it was continued with renewed interest, and the results are given below. For the original suggestion of the work I am indebted to Dr. Warthin, who gave me access to the material of his laboratory, and my research has, from time to time, been controlled by him. The material examined consisted of 30 cases of cancer of the breast infiltrating the pectoral muscle, 15 cases of epithelioma of the lip, 1 of cancer of the tongue, 1 case of lupus-carcinoma of the cheek, 2 secondary carcinomas of the diaphragm, 2 cases of sarcoma of the pectoral, 2 fibrosarcomas of the rectus abdominis, 2 sarcomas of the inferior maxilla, 1 sarcoma of fore-arm, 3 of femur, 1 of tibia, and 1 of general sarcomatosis of the skin. Examinations were made both of hardened and fresh material. Alcohol, mercuric chloride, Flemming's, Müller's, and Zenker's fluids were used as fixing agents. The muscle was cut both transversely and longitudinally. Celloidin and paraffin embedding were both employed; and the following stains were used: hæmatoxylin and eosin, Van Gieson, carmines, polychrome, methylene blue, orcein, Russell method for cell-inclusions, Weigert nerve method, Mallory's reticulum method, and Plimmer's method.

FIG. 1.



Carcinomatous nodule in pectoral muscle, showing manner of invasion. (Leitz obj. 3, eye-piece III.)

MANNER OF INVASION. 1. *Carcinoma in Pectoral Muscle.* The primary carcinoma of the mammary gland advances by direct expansion until the fascia of the pectoral muscle is reached. The latter serves as a barrier to further advance, and the carcinoma usually reaches the muscle through the lymphatics. Uninvolved fascia may separate the main mass of the tumor from the muscle when in the latter there are metastatic foci of tumor-cells in the lymph vessels about the bloodvessels. Serial sections show that these are often not metastases, but direct extensions of the growth through the vessels. When the nodules in the muscle reach a large size the muscle-fascia may be destroyed, but in the earlier stages it is rarely involved. Its normal appearance is, however, no evidence that there are no tumor nodules in the muscle beyond it. The muscle may be strewn with nodules varying in size from a pin-point to a walnut. They resemble the primary in structure. Arising in the interstitial tissue, they push the muscle-fibres apart and produce in it the most varied pathological changes. As the nodules increase in size there is more or less complete destruction of the fibres. Remains of these may be found in the cancer nodule. In infiltration with scirrhous carcinoma there is a marked proliferation of the perimysium, and this leads to the production of marked changes in the primitive bundle. Small islands of muscle-protoplasm and small groups of cancer-cells are surrounded by a dense mass of connective tissue. Invasion by way of the bloodvessels is rare. When the muscle is once reached further extension takes place through the lymph-spaces of the interstitial tissue and also through the sarcolemmar tubes.

2. *Epithelioma of the Lip.* The invasion of muscle is favored in this region by the structure of the muscle-fibres, these being short and irregular and the perimysium of a very loose texture. The irregular columns of epithelial cells fill in the meshwork of the perimysium; the younger cancer-cells infiltrate between the separate muscle-fibres and destroy these as they increase in size. Leucocyte infiltration is usually marked, and it is difficult to separate the leucocytes from the young cancer-cells. Cells undergoing hyaline change or cornification may also be mistaken for remnants of muscle. Small fragments of muscle-plasma and nuclei may sometimes be found in the central portion of a cancer nest; this appearance is, however, explained by the plane of the section, and is not due to an encapsulation of muscle by cancer-cells as has been supposed. Penetration of the sarcolemmar tubes by the young cancer-cells also occurs, but is more rare than in the case of breast cancer.

3. The invasion of muscle by secondary carcinoma in other regions is similar to that in these two places, the difference depending upon the local conditions in the muscle and the character of the tumor-cells.

4. *Sarcoma.* The invasion of muscle by sarcoma takes place by direct extension in the form of outgrowths of the main mass penetrating the muscle-bundles, extension of slender cords of cells between the

muscle-fibres, and also by lymphogenous and hæmatogenous metastasis. There is always much less reaction in the perimysium of muscle invaded by sarcoma than there is in the case of carcinoma. The ingrowths of sarcoma replace the perimysium, at first separating the muscle-bundles, which may show but slight change. As the proliferation of the tumor progresses there is gradual atrophy and disappearance of the muscle-fibres. These may, however, persist for a long time, and not infrequently small bits of muscle may be found scattered throughout the tumor. Many of these may appear as regeneration forms. In the case of universal sarcomatosis of the skin, large subcutaneous nodules were present which resembled greatly enlarged lymph-glands. On section these were found to contain in their central portion the remains of muscle-fibres. Round-cell sarcoma produces a more rapid destruction of muscle than the spindle-cell variety. On the whole the effects of the invasion of muscle by sarcoma appear to be chiefly mechanical, as the surviving bits of fibres usually show but little change in structure. The rapidity of growth in some cases causes a rapid disappearance of the muscle without preceding retrograde changes.

CHANGES IN MUSCLE PRODUCED BY INVADING MALIGNANT TUMOR. 1. *Atrophy.* This is the most frequent and constant change. It may be either mechanical or chemical in nature. In the case of scirrhous carcinoma, epithelioma, and sarcoma, the atrophy is limited to the area of muscle invaded by the growth, and is chiefly the result of pressure. In the case of non-scirrhous cancers of the breast, the atrophy may extend into the pectoral a long distance from the advance cells of the tumor, and may affect large bundles of muscle in which no cancer-cell is present. This cannot be explained as mechanical in origin; on the other hand, it is probable that it is due to disturbed biological or chemical relations. Both forms of atrophy may be present in the same case, but the chemical form is more characteristic of carcinoma. In scirrhous carcinoma, epithelioma, and sarcoma the length of the muscle-fibre is very frequently preserved, while its thickness is reduced to that of a mere thread. In the rapidly growing forms of breast cancer the fibres of the pectoral show great variation also in length.

2. *Hypertrophy.* The occurrence of hypertrophic fibres in the neighborhood of malignant growths was maintained by Schaeffer, who made measurements of the fibres in 2 cases of fibrosarcoma. But even in the case of actual measurements it is hardly possible to make such a diagnosis, inasmuch as the standard of size shows such individual differences. Large fibres occur very frequently among the atrophic ones, but this enlargement in the majority of cases is only relative. The size of the fibre is also increased in certain forms of degeneration, notably cloudy swelling.

3. *Changes in Morphology.* Very marked and varied changes in the morphology of the fibres occur. The parallel arrangement of the fibres

may be changed; they may be bent at various angles, often assuming a spiral form. The sarcolemma may be retracted from the muscle-substance, the latter being formed into wavy bands or broken up into scroll-like figures.

4. *Changes in Muscle-substance.* (*a*) *Alteration in the Striation.* In the atrophic fibres the cross striation is usually very sharply defined, the alternating light and dark bands being very narrow. Very frequently there is a longitudinal fibrillation with loss of the cross striation. The plasma is divided up into its fibrillar elements, and often at the cut end of a fibre these may be seen protruding from the sarcolemma in a brush-like manner. Except in the case of cloudy swelling and Zenker's necrosis, the longitudinal striation persists as long as the plasma remains intact.

(*b*) *Vacuolization.* This is a frequent change, and in some cases may be the only one present. It occurs often as a very early sign of degeneration. The vacuoles appear as clear or cloudy spaces in the plasma, which contrast strongly with the surrounding stained plasma. They may be sharply outlined as if punched out, or their border may be irregular, in many cases appearing as if fringed. They vary much in size and shape, and at times communicate by delicate grooves or channels. When located at the periphery of the fibre the sarcolemma may bridge over the vacuole or become invaginated into it. In the majority of cases they are to be interpreted as due either to hydropic degeneration or Zenker's necrosis.

(*c*) *Fissuring.* Fragmentation of the fibre may occur in any plane, transverse, longitudinal, or irregular. These changes may be partly of the nature of an artefact, but are undoubtedly pathological to a large extent, as they occur in the most carefully fixed specimens.

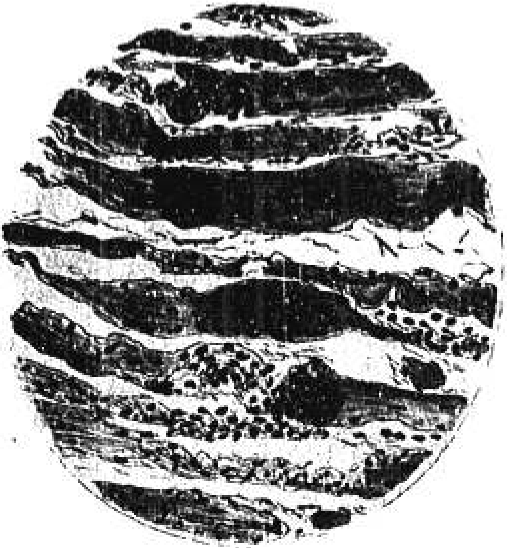
(*d*) *Waxy Degeneration.* Zenker's necrosis is of very common occurrence, particularly in the case of mammary cancer invasion of the pectorals, where it very often occurs at some distance from the tumor. Schaeffer maintained that this form of necrosis was not common near tumors, but in my cases it has been found both of frequent and extensive occurrence.

(*e*) *Cloudy Swelling.* This is of very frequent occurrence. The fibres are swollen, granular, stain heavily, and show a tendency to take both nuclear and diffuse stain (polychromatophilia).

(*f*) *Fatty Degeneration.* No fatty change was found in muscle in the vicinity of tumors, though repeated search was made with the use of osmic acid. Weber and Schaeffer state that it is of common occurrence under these circumstances, but Fujinami found only traces of it in the examination of fresh material.

Lacunar Erosion. The appearances described by Volkmann under the head of "lacunar erosion" occur not infrequently in invading carcinoma of the pectoral. Muscle-fibres which otherwise may appear normal present one or more cup-shaped indentations of the plasma at some point along its margin. These depressions usually contain eight to twelve nuclei, which are small and irregular in outline, but from general appearances must be considered to be muscle nuclei. Other fibres may be found in which the muscle-substance is intact except at one or both poles, where it is interrupted by a concavity which may be shallow or deep. In these depressions are numerous deeply staining nuclei packed so closely that, with the low power, their character cannot be made out. Examination with high powers shows that the sarcolemma is prolonged for some distance beyond the muscle-substance, the two lines representing the cross section of the sarcolemma finally converge and meet. These apparent erosions are, therefore, explainable as being portions of the fibre where the muscle-substance has entirely disappeared as the result of degeneration, while the muscle nuclei have undergone proliferation. Other fibres show earlier stages of this process; beneath the sarcolemma the remains of the muscle-substance,

Fig. 2.

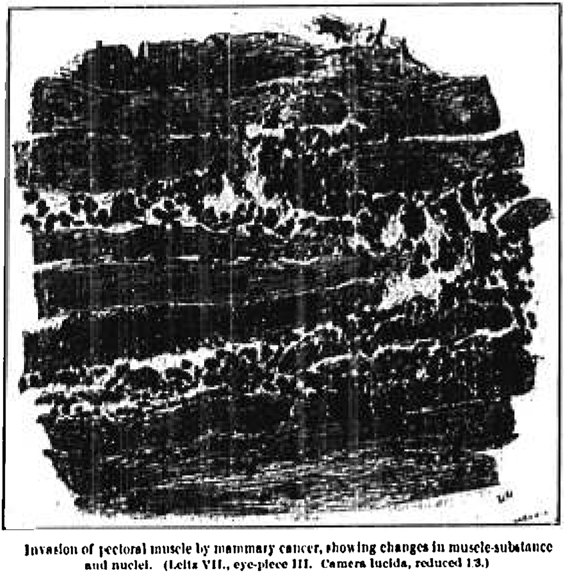


Pectoral muscle near periphery of mammary carcinoma, showing lacunar erosion and ampullar atrophy. (Leitz VII., eye-piece III.)

in the shape of granular detritus tinged with diffusely staining chromatin, are found. These apparent erosions are in the majority of cases not due to the presence of tumor-cells, but in some instances a group of the latter is found pushing the sarcolemma into the depression and presenting the appearance which led Volkmann to believe that the erosions were due to an "eating-out" action on the part of the tumor-cells.

5. *Changes in the Muscle Nuclei.* (*a*) *Proliferation.* This is a very common change, and presents many features of unusual interest.

FIG. 3.

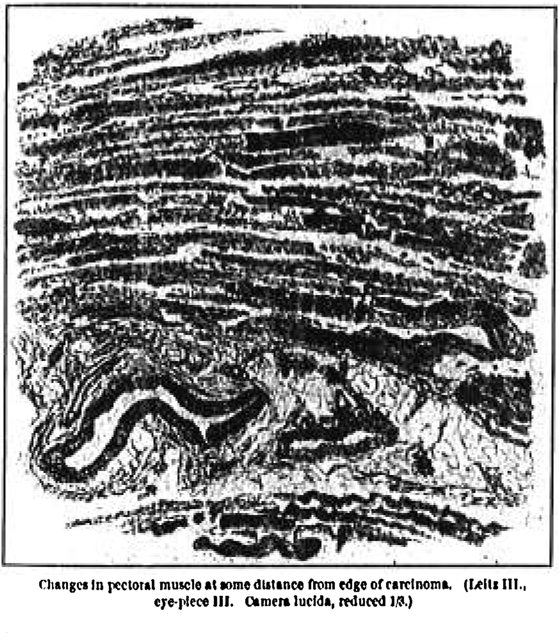


Invasion of pectoral muscle by mammary cancer, showing changes in muscle-substance and nuclei. (Leitz VII., eye-piece III. Camera lucida, reduced 1:3.)

Increase in the number of the nuclei leads to the formation of long nuclear chains, often sixty nuclei being counted in one chain. At other times they may be so numerous as to form a solid cord. In transverse sections the nuclei are often seen arranged in clumps replacing a portion of the plasma just beneath the sarcolemma. The central portion of the fibre may contain many nuclei. The collections of nuclei found in the cup-like erosions of the muscle-substance beneath the sarcolemma are undoubtedly muscle nuclei which have multiplied at these points. Waldeyer has described appearances in diseased muscles in which the protoplasm is entirely replaced by muscle nuclei (Muskelschlaüche). In a few instances these were found by me, but were not so typical as suggested by some observers. No mitotic figures were found in any of my specimens, the proliferation appearing to be by direct division.

(*b*) *Changes in Morphology.* The normal muscle nucleus is oval in shape, and the average measurement is 7 to 11 μ in length and 3 to 4 μ in breadth. Near malignant tumors they become very much elongated, some nuclei measuring 40 μ in length. Others are very short, some atrophic, and others hypertrophic. They may be very much altered in shape and staining power. The nuclei survive the destruction of the muscle-substance, but ultimately disappear also.

FIG. 4.



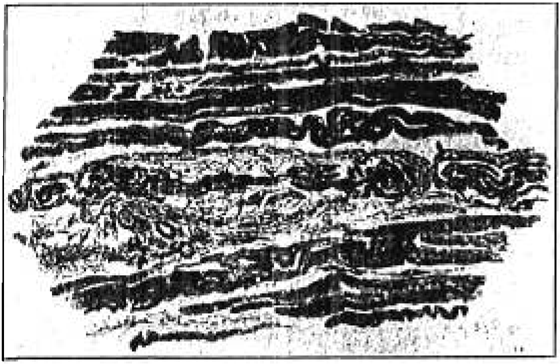
Changes in pectoral muscle at some distance from edge of carcinoma. (Leitz III., eye-piece III. Camera lucida, reduced 1/3.)

6. *Changes in the Sarcolemma.* The behavior of the sarcolemma during the destruction of the muscle protoplasm has already been men-

tioned. Its final fate is degeneration and complete disappearance, though some investigators believe that it may take part in the proliferation of the perimysium. After the disappearance of the muscle-substance the sarcolemmar tube may collapse or it may be entered by leucocytes and tumor-cells. Not infrequently it appears to have been distended by fluid.

7. *Changes in the Perimysium.* In infiltration of the perimysium with cancer-cells the connective tissue takes part in the formation of the stroma of the cancer nodule. The proliferation of the perimysium takes place, however, to a much greater extent in the case of spindle-cell and fibrosarcomas, epithelioma, and scirrhous cancer than in carcinoma simplex or medullare. Secondary changes such as fatty infiltration, leucocyte infiltration, hemorrhage, œdema, necrosis, etc., are of common occurrence in the interstitial connective tissue.

FIG. 5.



Muscle spindle in pectoral muscle near invading carcinoma, showing nuclear proliferation in intrafusal fibres near equator. Neighboring muscle shows retrograde changes. (Leitz III., eye-piece III. Camera lucida, reduced 1/3.)

8. *Vascular Changes.* Obliterative endarteritis and periarteritis are of very frequent occurrence, and in the majority of instances are due to local changes. Proliferation of the endothelium of the lymph-channels was seen in a few cases. The vascular changes are most pronounced in the larger vessels.

9. *Changes in Nerve Elements.* Sections stained according to Weigert's method showed no change. Fujinami describes a connective-tissue increase in the nerve-trunks, but this was not seen in my material.

Special search was made for possible changes in the muscle-spindles, as these organs have not hitherto been considered in this connection. Forster studied the behavior of the spindle in many pathological conditions, such as acute myelitis, progressive muscular atrophy, etc. With the most marked change in the muscle he found the spindle remaining normal. Sherrington found no changes in the spindle to be produced by cutting muscles and tendons. Batten found a spindle which stained poorly in a case of tabes dorsalis, and in a case of atrophy and degeneration of the upper arm muscles, due to injury of the brachial plexus, the spindles were atrophic, the intrafusal fibres showed granular degeneration, the spindle sheath hazy, and the nerve-fibres of the spindle degenerated. Grünbaum found a peculiar hyalin deposit around the intrafusal fibres in a case of pseudohypertrophy. In my own work many preparations were examined for the study of the spindle. The nerve-trunks leading to the spindle were normal in every case examined. In one case of pectoral carcinoma longitudinal sections of a spindle showed a marked nuclear proliferation in the intrafusal fibres near the equator, but as similar appearances have been seen by several observers in apparently normal spindles the significance of this appearance is not clear.

10. *Small-celled Infiltration.* Leucocyte infiltration is found to some extent in or about all malignant growths. It is very marked in the case of epithelioma of the lip, but occurs to a very slight degree about invading cancer of the pectoral. The leucocytes are for the greater part collected about the bloodvessels and along the border-line of the invading growth. They are usually found intermingled with young tumor-cells, and it is difficult and often impossible to distinguish between the two.

11. *Occurrence of Mast-cells.* Both leucocyte and connective tissue mast-cells were at times found abundantly in the areas where small-celled infiltration was most marked. In a few instances mast-cells were found inside the sarcolemmar tube in company with other forms of leucocytes. In some of the cases of mammary cancer large numbers of eosinophiles were present in the areas of small-celled infiltration of the perimysium.

12. *Regeneration of Muscle.* In two-thirds of the cases of sarcoma and in three cases of epithelioma cell-forms identical with those seen in the repair of muscle were found in large numbers. They were never seen in the pectoral muscle in carcinoma, but were very numerous in a case of spindle-cell sarcoma of that muscle. The new fibres are found in the stroma of sarcoma and in the granulation tissue at the periphery of lip-epithelioma. The newly-formed fibres are usually short, and are spindle or club-shaped, or irregular in form. Their protoplasm stains well with eosin. The nuclei are numerous and are usually

grouped at one extremity. Many of the new fibres are vacuolated, their nuclei large and vesicular, and their protoplasm taking both nuclear and diffuse stains. These evidences of degeneration are exactly similar to those occurring in the new fibres after repair of muscle wounds. Fujinami, however, interprets the forms found near malignant tumors as being essentially degenerative in nature and not regeneration forms. He explained their formation as follows: The degenerating fibre is constricted at regular intervals, and this constriction goes on until the fibre is broken up into fragments, the nuclei at the same time proliferating ("ampullar atrophy"). The muscle-fragments he calls "ampullæ," and these he considers to be larger and to possess larger and more deeply-staining nuclei than the true muscle-buds in regeneration. While it is very probable that muscle giant-cells may be formed by the disintegration of the fibre, this explanation will not hold for my cases. In these, serial sections show that the giant-cells are really muscle-buds and not muscle-fragments. Their arrangement is not at all in accord with the idea that they are degenerating remains of old muscle. The presence of vacuoles in protoplasm and nuclei is also no argument that they are essentially degeneration forms, as it is well known that the newly-formed fibres in the repair of muscle wounds also quickly undergo degeneration, and do not lead to the production of muscle capable of functionating. I regard the appearances found in my cases as identical with those found in muscle repair.

SUMMARY OF CHANGES WITH REFERENCE TO THE DIFFERENCE BETWEEN THOSE PRODUCED BY SARCOMA AND CARCINOMA. 1. *Atrophy.* This is more marked in the case of carcinoma. In sarcoma the muscle may show an extreme degree of pressure atrophy at the border of the tumor, but in carcinoma there is usually a general atrophy, even of fibres at some distance from the cancer. This can be interpreted as chemical or toxic atrophy. I have not seen it in sarcoma.

2. *Hypertrophy.* This was not seen in any of the cases of carcinoma, but in a case of spindle-cell sarcoma of the pectoral the muscle-fibres appeared unusually large.

3. *Morphological Changes.* These are much more marked in the case of carcinoma, the muscle-fibres often assuming very grotesque forms. In sarcoma this distortion occurs to a very slight degree. The changes in carcinoma are so constant, even with the most careful technique, that they cannot be regarded as artefacts. The finding of mast-cells and leucocytes within the sarcolemma is also evidence that these changes occurred during life.

4. *Change in Striation.* Longitudinal fibrillation was present in all of the carcinoma cases; in sarcoma it was seen only rarely.

5. *Vacuolization.* This is a frequent and early change in both sarcoma and carcinoma.

6. *Retrograde Changes.* Early stages of cloudy swelling are common in the case of sarcoma, but in carcinoma the degeneration is more frequent and much more severe. Zenker's necrosis is of much more frequent occurrence in the case of carcinoma, in the pectoral often occurring at a distance from the tumor.

7. *Lacunar Erosion.* This form of degeneration of the muscle-substance is almost characteristic of carcinoma, being found only in one form of sarcoma, small round-cell of the skin. It may be emphasized once again that this so-called erosion is independent of any mechanical action of tumor-cells; but is a primary change in the muscle-substance.

8. *Nuclear Proliferation.* An increase in the number of the muscle nuclei is very commonly found in carcinoma, but often absent in sarcoma, even when other degenerative processes are present. This is in accord with the fact that the muscle-substance in sarcoma shows a much less tendency to retrograde changes. Nuclear proliferation goes hand-in-hand with degeneration of the muscle-substance. This apparent paradox may be explained on the hypothesis of a reversion to an embryonal state antecedent to degeneration, or that the normal muscle-substance has an inhibitory influence over the nuclei, the removal of which in degeneration of the former permits an unrestrained proliferation of the latter. Changes in size and form of the nucleus go hand-in-hand with nuclear proliferation.

9. *Sarcolemma.* Changes in this are more manifest in carcinoma because of the more marked changes in the protoplasm.

10. *Vascular Changes.* These are very common in both carcinoma and sarcoma; if anything, more marked in the case of the former. Hypertrophy of the endothelium occurs more commonly in sarcoma.

11. *Small-celled Infiltration.* This is very marked in lip-epithelioma, but in pectoral carcinoma it is very often very slight or entirely absent. In sarcoma the leucocytes were not numerous in the muscle and were usually limited to the perivascular areas of the perimysium. The enormous infiltration in lip-epithelioma may be due to secondary inflammation or infection, the location favoring the occurrence of these events.

12. *Muscle Regeneration.* As mentioned above, this was found only in the cases of sarcoma and lip-epithelioma. It was never seen in pectoral carcinoma.

From this summary it is evident that the muscle changes occurring near carcinoma and sarcoma are not identical, as claimed by Schaeffer and Fujinami. This observation is of great interest because of the significance which may be attached to it. The essential difference between the two may be briefly stated as follows: Retrograde changes are marked in the case of carcinoma; in sarcoma they occur to a very slight degree, or may be entirely absent. In sarcoma the atrophy is apparently only mechanical, while in carcinoma it occurs at a distance from the tumor under conditions which make it very probable that it is of a toxic nature or due to a withdrawal of nutrition. The morphological changes in the muscle-fibre are more marked in carcinoma than in sarcoma, and this may be explained in the same way. Nuclear proliferation is marked in the case of carcinoma, in sarcoma it occurs to a slight degree, and in the majority of cases is absent. Regeneration forms are numerous in sarcoma, but were never found in pectoral carcinoma. Their presence in lip-epithelioma may be due to the extensive inflammatory changes present.

Comparing the changes produced in muscle by malignant tumors with those due to other causes, we find that the differences are of degree rather than of kind. Krauss, in experimental work on animals, found that sections of the nerve-trunks produced atrophy, nuclear proliferation, cloudy swelling, loss of striation, and vacuolization. Normal and diseased muscle-fibres were found side by side. Changes similar to these occur in acute anterior poliomyelitis, the bulk of the muscle being replaced by fat and connective tissue. In primary myopathy the fibres are atrophic or completely degenerated, occasionally hypertrophic (?) fibres are seen. The cross striation is indistinct, longitudinal fibrillation is marked, and fissuring, vacuolization, increase of connective tissue, fatty infiltration, and leucocyte infiltration are also present. In progressive muscular atrophy the fibres are much reduced in thickness, their striation is coarse or indistinct, with a tendency to fissuring; longitudinal fibrillation is common, and there is marked fatty degeneration, the sarcolemma often being filled with fat-droplets.

If the changes produced by malignant tumors show nothing specific in character, to what may the great difference in degree between those due to carcinoma and sarcoma be referred? The local changes in muscle invaded by tumors may be explained as due either to direct pressure of the tumor-cells or to chemical and nutritive influences. The difference between the two types may be the result of their different biological relations. Carcinomata are epithelial in origin, sarcomata mesoblastic, the invaded tissue muscle is also mesoblastic. An abnormal proliferation of any tissue means marked metabolic changes, the consumption of much nutritive material, and the giving off of much waste product. Tumor-cells behave in a manner similar to that of parasites, invading another complexus of cells, and flourishing at the expense of the latter. The tissue invaded suffers both from loss of nutrition and from the effects of the metabolic products of the more actively proliferating tumor-cells. Whether specific poisons are produced by the latter we are not yet in a position to say, but the changes about carcinoma are for the greater part to be interpreted as toxic in nature. In the invasion of muscle by sarcoma the antagonism between the two tissues must be less marked than in the case of carcinoma. The sarcoma cells are genetically mesoblastic, and have similar capacities and tendencies to those of muscle. Hence, a sarcoma may infiltrate the entire perimysium and produce no changes except the simple atrophy due to mechanical pressure. In the central portion of a large sarcoma mass remains of muscle-fibres may still be present and may present no retrograde changes. Such an occurrence I have never seen in carcinoma; here the invaded muscle is quickly destroyed. The attempts at regeneration found in sarcoma are also an evidence of the less injurious effects of the latter. Carcinoma is, therefore, more antagonistic of muscle than sarcoma, because of its different biological relations, the different nutritive and metabolic conditions, and also probably because of the formation of poisonous products by the cancer-cells.

CONCLUSION. 1. The changes produced in striped muscle by invading malignant tumors are:

A. Retrograde.
  1. Atrophy.
  2. Morphological changes.
  3. Changes in protoplasm.
     Vacuolization.
     Fissuring.
     Longitudinal fibrillation.
     Lacunar erosion.
     Cloudy swelling.
     Simple necrosis.
     Zenker's necrosis.
     Polychromatophilia.
  4. Changes in nucleus.
     Morphological changes.
     Proliferation.
     Vacuolization.
  5. Perimysium.
     Atrophy.
     Hyperplasia.
     Leucocyte infiltration.
     Hemorrhage.
     Œdema.
     Necrosis.
  6. Vascular changes.
     Endarteritis.
     Periarteritis.
     Hypertrophy and hyperplasia of endothelium.

B. Regenerative.
  1. Hypertrophy (?).
  2. Regeneration forms.

2. These changes are not specific, but are produced by conditions other than malignant tumors.

3. The changes produced in muscle by invading carcinoma are more marked than those produced by sarcoma, but do not differ essentially in kind. Those produced by sarcoma are chiefly mechanical; those due to carcinoma are mechanical, nutritive, and metabolic. Evidences of toxic action are more marked in the latter than in sarcoma. Carcinoma acts more as an active injurious foreign body upon muscle than does sarcoma.

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A CASE OF OPHTHALMIA NEONATORUM CAUSED BY THE DIPLOBACILLUS OF MORAX AND AXENFELD.

By E. ANDRADE, M.D.,
OF HAVANA, CUBA,
EX-ASSISTANT TO THE OPHTHALMIC CLINIC OF THE UNIVERSITY OF GENOA, ITALY.

THAT the gonococcus is not the only cause of ophthalmia neonatorum is a conceded fact. The diplococcus, the streptococcus, the bacillus coli communis, and the micrococcus aureus also produce purulent conjunctivitis in the newborn. The last statistics of Groenouw show that in one hundred cases of ophthalmia neonatorum the gonococcus was present in only forty-one. All observers agree, however, in the opinion that when the disease is due to the gonococcus it usually assumes a very severe character.

Among the several micro-organisms described in connection with purulent conjunctivitis of the newborn the bacillus of Weeks and the diplobacillus of Morax and Axenfeld have never been mentioned. Having met with an unusual case of ophthalmia neonatorum caused by the last-named bacterium, which as a general rule is only found in cases of subacute catarrhal conjunctivitis, I have deemed it of sufficient interest to report.

Clinical History. E. L., female, three days old, child of healthy parents, presented slight œdema of the lids and a small amount of purulent exudate in both eyes, the symptoms being more marked in the right eye. There was no chemosis. The parents asserted that their two other children had shown, shortly after birth, similar symp-